National Institute of Neurological Disorders and Stroke: Developing a Manual of Procedures (MOP)

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1.0 INTRODUCTION

The National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), must ensure compliance with Federal law and regulations, including procedures and policies to protect the safety of all participants in the clinical studies it supports. This template for a Manual of Procedures (MOP) is designed to help clinical investigators comply with NIH regulations and procedures and promote high quality research. The MOP transforms a protocol into an operational research project. It documents study flow so that the screening, initial evaluation, enrollment, randomization, treatment, and follow-up of all study participants are conducted in a structured and standardized manner. It details how the data are observed, collected, and recorded. It specifies quality control procedures, and it defines methods for ensuring confidentiality of participant information. The MOP is written in sufficient detail such that it could be used as a training manual for new study investigators.

The MOP is a dynamic document that is updated throughout the study to record amendments to the protocol or consent forms, and to document refinement of procedures. It is maintained in a format that allows it to be easily updated, typically in a three-ring binder. The version number and date should appear on each page of the MOP to track all changes and additions to the document. Revised pages replace the original pages as they are updated. All previous versions should be archived.

The MOP development process must involve the investigators and study staff to ensure that the study will be performed as intended. In multiple site clinical studies, a Steering Committee, composed of the Principal Investigators from each of the sites, is often appointed to finalize the protocol and elements of the MOP.

2.0 MOP CONTENTS AND ORGANIZATION

The MOP typically includes the following sections:

a. Study Protocol
b. Roster
c. Study Organization and Responsibilities
d. Recruitment, Screening, and Eligibility Criteria
e. Informed Consent
f. Randomization
g. Blinding and Unblinding
h. Study Intervention
i. Subject Evaluations and Follow-up
j. Study Completion
k. Concomitant Medications
l. Safety Reporting
m. Data and Safety Monitoring Activities
n. Study Compliance
o. Data Collection and Study Forms
p. Data Management
q. Quality Control Procedures
r. Policies
s. MOP Maintenance

The above sections apply not only to drug intervention studies, but also to surgery, behavioral, and device studies. In studies where a section does not apply (e.g., randomization in a study with no randomization), the study investigators need not include it in the MOP. Each of the above MOP sections is now described.

2.A STUDY PROTOCOL

The final version of the study protocol with the date of approval and version number, is often included in the MOP. See http://www.ninds.nih.gov/funding/clinical_trials/protocol.htm for a detailed discussion of protocol development,

2.B ROSTER

The roster includes the names, roles, addresses, phone numbers, fax numbers, pager numbers, and e-mail addresses of study staff, committee and DSMB members, and NINDS staff.

Information on whom to contact regarding the following study procedures should also be included:

- randomizing a participant
- reporting a serious adverse event
- requesting additional supplies

In addition, information on whom to contact regarding the following uncommon special situations should also be included:

- requesting an exemption to study protocol for an individual study participant
- unblinding a participant

2.C STUDY ORGANIZATION AND RESPONSIBILITIES

This section of the MOP describes the organization and responsibilities of the study centers and committees. Multicenter studies, especially Phase III studies and other large studies, may have a Coordinating Center that is responsible for the development of the study materials and oversight of study operations. The Coordinating Center may also be responsible for the study's statistical aspects, including the statistical plan and data analyses; or there may be a separate

statistical center. Other studies may be organized to include a clinical Coordinating Center, data management center, and statistical center. Additionally, there may be central laboratories and study committees. Organization charts help to clarify organizational responsibilities and roles.

Study organizational responsibilities may include:

- development and maintenance of the MOP
- randomization scheme and procedures
- development and implementation of data flow, schedules for transferring data from sites, and data tracking
- development of procedures for data entry, error identification and correction
- safety monitoring and reporting
- communications with clinical sites, such as scheduling meetings and training sessions; responding to and documenting ad hoc communications
- site visits to ensure adherence to the protocol and procedures
- quality control
- reports, such as enrollment, adverse events, participant status (e.g., drop-outs)
- distribution of all changes, updates and policies of above mentioned reports and documents to all participating clinical sites
- preparation of materials and reports for the Data and Safety Monitoring Board (DSMB)

Some studies have lead sites that take on study coordination responsibilities. In single-site studies, study staff members have the responsibility for activities in this section as well as for those in the following section (2.c.1).

2.c.1 Clinical Sites

The roles and responsibilities of the Investigators and Clinical Sites may include:

- participating in protocol finalization and preparation of study materials
- assuring that the study is conducted according to the protocol and MOP
- participating in a Steering Committee and other study committees
- identifying, recruiting, screening and enrolling subjects
- protecting participants' rights
- obtaining informed consent from each subject
- collecting study data and following participants through study completion
- controlling the distribution of the drug intervention under study for drug treatment studies
- retaining specific records (e.g., laboratory drug distribution records)
- preparing and sending required reports to Coordinating Center (e.g., recruitment and enrollment, gender and minority breakdowns, adverse event reports), assuring IRB review and approval
- communicating questions, concerns, and/or observations to the Principal Investigator and/or Coordinating Center

2.c.2 Pharmacy Activities

“Pharmacy” refers to the unit responsible for the storage, dispensing and accountability for the investigational agent. An actual pharmacy may or may not be directly involved in a study at the clinical level. For example, in some studies the investigational agent may be delivered in pre-labeled, sealed packages directly to the clinical centers.

This section of the MOP describes how the investigational agent is to be stored, prepared, dispensed, and returned to the Sponsor. It provides instructions for completing drug accountability records and administration records.

2.c.3 Steering Committees

In some large multicenter studies, the Steering Committee is generally responsible for the overall direction of a study and is the main leadership committee. Frequently, the Steering Committee is typically comprised the clinical and Coordinating Center Principal Investigators.

The following areas typically fall under the purview of the Steering Committee:

- general design and conduct of the study and preparation of the essential study documents, including the protocol, MOP, and data collection forms
- review of data collection practices and procedures
- changes in study procedures
- appointments to and disbanding of study implementation subcommittees
- allocation of resources based on priorities
- review of study progress
- review and implementation of recommendations from the DSMB
- Review and response to other general advice and/or recommendations (e.g., from the NINDS Program Director)

2.D RECRUITMENT, SCREENING, AND ELIGIBILITY CRITERIA

This section of the MOP describes the target population, recruitment strategies, screening procedures, and eligibility criteria. The target population is the subset of the population at large from which study participants will be selected. Inclusion and exclusion criteria further define eligibility for participation.

2.d.1 Pre-Screening and Screening

This section provides a detailed discussion of all screening procedures outlined in the protocol to determine study eligibility. Frequently, there is a *pre-screening* phase during which the study coordinator reviews the investigator's patient medical records or responds to initial telephone inquiries from physicians or potential study participants. Pre-screening may be performed prior to obtaining the individual's informed consent. If the individual meets the pre-screening criteria, then he or she must sign an informed consent (see Section 2.E.) before screening procedures such as performing a physical exam and obtaining the individual's demographic information, medical history and laboratory results can continue.

A Screening Log documents the enrollment status of individuals. It generally contains individuals' initials, identification numbers, age, gender, race, date and time of hospitalization or office visit, eligibility status (i.e., eligible for study participation, ineligible for study participation and why, or if they refuse consent), and randomization numbers if applicable. The MOP describes the contents of the Screening Log and procedures for maintaining it.

2.d.2 Eligibility Criteria

Inclusion and exclusion criteria are protocol-specific and are outlined in the study protocol. Participants must meet all entry criteria prior to enrollment. This section clarifies any of the eligibility criteria that may not be specifically defined in the protocol or are subject to interpretation. It should also specify the forms needed to document eligibility (e.g., medical history form, physical examination form, laboratory form). All data captured on the forms to support the participant's enrollment in the study must be verifiable in the participant's source documents.

Although exemptions to study criteria are discouraged, there are some situations in which an exception to entry criteria may be sought. Thus, the procedures necessary for seeking an exemption, including the name and contact information of the person authorized to grant exemptions, should be provided, if relevant.

2.E INFORMED CONSENT

Informed consent is a process that involves:

- providing participants with adequate information concerning the study procedures and scope
- providing adequate opportunity for an individual to consider all available options
- responding to individuals' questions and concerns
- ensuring that each individual understands all information provided
- obtaining the individual's written voluntary consent to participate

NINDS-funded clinical studies are governed by 45 CFR 46, which specifies the contents of informed consent documents. In short form, the regulations call for:

- a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- a description of any reasonably foreseeable risks or discomforts to the subject;
- a description of any benefits to the subject or to others which may reasonably be expected from the research;
- a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and

whom to contact in the event of a research-related injury to the subject; and

- a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (45 CFR 46, Section 117)

Additional items that should be included in an informed consent document include:

- Complete disclosure of any appropriate alternative procedures, risks, benefits and any risks/benefits of the alternatives
- Disclosure of the extent of confidentiality that will be maintained
- Statement of compensation and/or medical treatment available if injury occurs
- Name, address, and telephone number of the Principal Investigator

The informed consent regulations are administered by the Office of Human Research Protections (OHRP), whose web site (http://ohrp.osophs.dhhs.gov) also provides an 18-item checklist to guide investigators in developing informed consent documents.

2.e.1 Informed Consent Process

Specific instructions regarding the process of obtaining informed consent must be detailed in this section. The study investigator or nurse coordinator typically provides a detailed explanation of the study and informed consent form to a prospective participant. Additionally, there should be a discussion of the nature of the study, randomization and blinding, study procedures, importance of compliance, potential risks and benefits, and duration of the study. The process should provide for ample time for the prospective participant to read the informed consent form.

An individual must be informed that he/she is not obligated to participate in the study. The informed consent process should ensure that there is no penalty for *not* participating in a clinical trial and that treatment will not be compromised if individuals do not participate or if they cease participation at any time. Adequate time should be allowed for the prospective participant to ask questions. The instructions must discuss the following:

- ***Study withdrawal*** - the protocol-specific study withdrawal process emphasizing that study participation is voluntary
- ***Signing the Informed Consent Form*** - the necessary signatures based on the site's IRB requirements (i.e. the participant's signature/legal representative, the investigator or person actually obtaining the consent, and a witness).
- ***Maintaining the Informed Consent Form*** - where the informed consent form should be maintained and to whom a copy of the form should be provided.

2.e.2 Informed Consent Document

The written Informed Consent form should be brief and written in plain language so that an individual who has not graduated from high school can understand the contents. Consent documents should be written with the assumption that prospective participants will not talk to a researcher or research nurse about the study, and that their information will come entirely from the consent document. If this approach is used, the document is more likely to be clear, complete, written for non-scientists, and able to "stand alone."

The Principal Investigator, participant, and witness must each sign and date the Informed Consent Document. The Principal Investigator, study nurse and a witness should be present when the participant signs the informed consent document.

The International Committee on Harmonization (ICH) Good Clinical Practice (GCP) guidelines require that the participant or legal representative receive a copy of the signed and dated informed consent form. OHRP and the Food and Drug Administration (FDA) both require that the participant receive a copy, although it may not necessarily be a signed copy. Additionally, the investigator must maintain a signed copy of the informed consent document for each

participant in the study. The source documents should indicate that the informed consent form was signed, along with the date of signing.

If there is a change in any of the study procedures that may affect the participant, the informed consent document must be revised and approved by the IRB. Any participants enrolled in the study prior to such changes must sign the amended consent form.

2.F RANDOMIZATION

The MOP should describe the study randomization approach, as relevant. In randomized clinical trials, participants are assigned to a treatment group based upon a predetermined randomization scheme developed by the study statistician. Randomization is introduced to reduce bias in treatment selection. This section of the MOP also provides a full discussion of the randomization procedures including:

- ***Process Responsibilities***: The individual who maintains the master randomization list at the Coordinating Center must be identified. This person is responsible for assigning randomization codes, notifying appropriate study staff that the subject has been randomized, and securely storing all randomization files.
- ***Procedure for Randomizing a Subject:*** At each site, the individual responsible for initiating the randomization procedure must be identified. This individual must know whom to contact once an individual is determined eligible for a study and which forms must be completed prior to randomization (e.g., informed consent form and subject eligibility form).
- ***Documentation of Randomization:*** The person responsible for completing the randomization log at each site must be named.

2.G BLINDING AND UNBLINDING

In most randomized studies, the study participants and the treating physician are "blinded" or "masked" to the treatment and do not know if the participant is receiving drug or placebo. The study statistician and/or a designated study staff member keeps the randomization assignment secure so that the treatment assignments are not known. Blinding and unblinding procedures should be clearly specified in this section of the MOP.

Unblinding is a serious action and should be performed only if necessary to ensure the safety of a study participant. The DSMB or Medical Safety Monitor must be involved in the decision to unblind and must grant approval for unblinding.
In the event that unblinding occurs, the following should be recorded:

- ID of unblinded participant
- reason for unblinding study staff
- person responsible for unblinding study staff
- list of person(s) who are unblinded (including the participant, if applicable).

2.H STUDY INTERVENTION

This section describes the study intervention in clinical trials. Interventions include drugs, surgery, devices, biobehavioral activities (e.g., coping mechanisms), and/or lifestyle changes (e.g., diet, exercise). All intervention studies require valid scientific evidence in order to determine if the intervention is safe and effective. The intervention, whether medical treatment, device, or behavioral, should be described thoroughly.

For ***drug intervention*** studies, the distribution, preparation and handling, labeling, and administration are detailed along with the duration of treatment and criteria for treatment discontinuation. A detailed description of the information that must be provided is documented in the ICH E6 Good Clinical Practice Guidelines. This document is available on the Internet at http://www.ich.org/pdfICH/e6.pdf

Device studies require a detailed description of the device and its intended use. Information on device studies is provided in the Code of Federal Regulations (CFR) Title 21, Parts 800-1299, revised as of April 1, 2000 (see http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfrv8_00.html).

For ***surgical*** studies, the procedure is described in detail.

Biobehavioral and ***lifestyle*** studies describe how the intervention is to be carried out.

2.I EVALUATIONS AND FOLLOW-UP

This section describes the baseline and follow-up evaluations and tests for enrolled participants. All evaluations, as well as their schedules and procedures for obtaining data, must be clearly stated in this section. All efficacy (e.g., visual analog scales) and safety evaluations (e.g., blood chemistries) should be defined. The schedule for evaluations must be specific (e.g., five hours after the last dose of study drug/placebo).

A useful study tool included in the MOP is a schedule of visits and evaluations. This schedule specifies what is to be done at each study phase and at each contact with the study participant. An example of a schedule is provided in Figure 1.

2.J STUDY COMPLETION

This section of the MOP describes the evaluations that take place at study completion, along with follow-up of participants who discontinue study treatment or drop out of the study. Participants should be followed to the end of the study, even if they discontinue treatment. The approach to following participants who discontinue treatment and the data that are to be collected should be detailed.

2.K CONCOMITANT MEDICATIONS

The MOP provides a discussion of which concomitant medications are allowed or restricted in the protocol. The form used to collect concomitant medication information and the period of time for which this information will be collected should be described. Concomitant medication information must be verifiable in the source documents.

FIGURE 1: Sample Time and Events for an NINDS Clinical Research Study

	Screening	Treatment Phase							Follow-Up Phase						
Study Visits	**-14 days to Day 0**	**Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Final Visit**
Informed Consent	X														
Medical History	X														
Prior Medications	X														
Physical Exam	X														X
Neurological Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistries	X														X
Liver Function Tests	X														X
Hematology	X														X
Pregnancy Test	X*														
Investigational Agent Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion Form															X

*Pregnancy test may be given more than once during the study.

2.L SAFETY REPORTING

This section of the MOP details the definitions of and procedures for reporting serious adverse events.

Relevant definitions include the following:

- ***Adverse Event (AE)*** - An AE is any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, whether or not related to the intervention. AEs include new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity.
- ***Serious Adverse Event (SAE)*** - An SAE is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects; or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.
- ***Unexpected Adverse Event*** - An unexpected adverse event is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product/device or package insert/summary of product characteristics for an approved product or device).

2.l.1 Adverse Event Reporting

Procedures for safety reporting are described in this section of the MOP. All AEs are collected, analyzed, and monitored by using an Adverse Event Form, a sample of which is shown in Figure 2. AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported. All AEs experienced by participants during the time frame specified in the protocol (e.g., from the time of study drug administration to 30 days following the last administration of study drug) should be reported.

2.I.2 Serious Adverse Event Reporting

Procedures for reporting SAEs are described in this section of the MOP. All SAEs, unless otherwise specified in the protocol and approved by the IRB, must be immediately reported by the Principal Investigator to the study's responsible group (e.g., DSMB or Safety Monitor, and NINDS). All interventional studies, independent of phase or type, must report SAEs. The immediate reports should be followed promptly by detailed written reports. An SAE does not need to be related to the study intervention to be reported.

2.M DATA AND SAFETY MONITORING ACTIVITIES

With increased concerns for participant safety, NINDS has established guidelines for data and safety monitoring activities for clinical trials it supports (see http://www.ninds.nih.gov/about_ninds/clusters/data_safety_monitoring.htm). A monitoring plan must be submitted and approved by the NINDS Program Director prior to the award for a clinical trial.

All clinical trials supported by NINDS must have a Safety Officer, Study Monitoring Committee, or a Data and Safety Monitoring Board (DSMB), depending upon the study phase, vulnerability of the study population, and risk of the intervention. Multicenter studies require a DSMB appointed by NINDS.

Data and safety monitoring activities are established to protect the safety of human subjects and maintain and ensure the scientific integrity of the study. Activities can include a review of the protocol with emphasis on data integrity and participant safety issues, monitoring of AEs, protection of the confidentiality of the data and monitoring of results, and recommendations to NINDS regarding continuation or conclusion of a study. For Phase II and III studies, the monitoring group is responsible for reviewing the study data at regular intervals, and determining if it is safe to continue the study according to the protocol. Although the DSMB's recommendations are advisory, they tend to carry great weight with NINDS Program Directors.

FIGURE 2: SAMPLE ADVERSE EVENT FORM

Study Name		
☐ Site:_____ ☐ Site:_____ ☐ Site:_____ ☐ Site:_____	**Participant Number** ☐☐☐☐☐ **Particpant Initials** ☐☐☐	**Date:** ___ ___ / ___ ___ / ___ ___ ___ ___ m m d d y y y y **Study Visit:** _____

Has the participant had any Adverse Events during this study? ☐ **Yes** ☐ **No** ***(If yes, please list all Adverse Events below)***

Severity	**Study Drug Relationship**	**Action Taken Regarding Study Intervention**	**Other Action Taken**	**Outcome of AE**	**Serious**
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely 2 = Probably 3 = Possibly 4 = Remotely 5 = Definitely Not 9 = Unknown	1 = None 2 = Discontinued Perm. 3 = Discontinued Temp. 4 = Reduced Dose 5 = Increased Dose 6 = Delayed Dose	1 = None 2 =Remedial Therapy-pharm 3 =Remedial Therapy-nonpharm 4 = hospitalization	1 =Resolved, No Sequela 2 =AE still present- no tx 3 =AE still present-being tx 4 =Residual effects present-no tx 5 =Residual effects present- tx 6 =Death 7 =Unknown	1 = Yes 2 = No (If yes, complete SAE form)

Event	Start Date	Stop Date	Severity	Relatedness	Action Taken w/ Study Drug	Other Action Taken	Outcome	Serious?	Initials

A Study Monitoring Committee (SMC) will be appointed by the Principal Investigator for trials not requiring a DSMB. The SMC typically consists of one or more members who are independent of the study operations. In addition, the Principal Investigator may be an ad hoc member of the group depending on the nature of the data being monitored. NINDS may appoint its own representative, and all monitoring procedures must be approved by the NINDS Program Director. The committee reviews safety issues and monitors AEs, especially SAEs.

2.m.1 Data and Safety Monitoring Responsibilities

A description of the roles and responsibilities of the Medical Safety Monitor, Study Monitoring Committee, or DSMB are described in this section. These entities monitor performance of the study, safety of participants, and efficacy. Monitoring *performance* of the study usually includes reviewing:

- patient recruitment
- flow of forms
- data quality
- adequacy of medical monitoring
- adverse event reporting
- protocol adherence
- appropriateness of protocol changes with regard to scientific integrity

Monitoring *safety* usually includes reviewing:

- risk of harm inherent in participating in the study
- adverse events (type, incidence, and severity)
- effect of protocol changes on risk

Monitoring *efficacy* usually includes:

- data review (blinded or unblinded)
- planned and unplanned interim analyses
- implementation of early stopping rule decisions

2.m.2 DSMB Membership

Members of a DSMB or SMC, and Medical Safety Monitors are selected to reflect a mix of appropriate clinical expertise and knowledge of the design, monitoring, analysis and ethical issues of the clinical research project necessary to protect participant safety and conduct a scientifically rigorous study. The DSMB members must also assure that they have no direct or indirect financial interest by signing a Conflict of Interest statement. (http://www.ninds.nih.gov/funding/clinical_trials/dsm_guidelines.htm).

2.N STUDY COMPLIANCE

Clinical trials are expensive endeavors, and procedures should be implemented to maximize adherence to the protocol, minimize participant non-compliance and enhance participant retention in the study. Drug accountability and other study procedures, such as ongoing communication between study staff and participant, to encourage participant compliance, are described in this section. Likewise, protocol violations and procedures to track them and notify appropriate parties must also be described in this section.

Protocol violations include but are not limited to the following:

- randomization of an ineligible participant
- failure to obtain informed consent
- entering a participant into another study
- failure to keep IRB approval up to date
- wrong treatment administered to participant

The MOP should describe relevant violations and the reporting process to all appropriate parties including the Principal Investigator at the study site, NINDS, and the DSMB or Medical Safety Monitor. Study staff should report a violation within 24 hours of occurrence or as soon as it is discovered. In addition, if site monitors discover any of these violations during a monitoring visit, they should notify NINDS of the occurrence in writing.

The Coordinating Center, lead site, or responsible person in a single site study should maintain a log of all protocol deviations and violations and should report them routinely to the DSMB, SMC, or Medical Safety Monitor. While there may be rational clinical reasons for an occasional violation, a site with serious continual problems is at risk for losing its funding.

2.O DATA COLLECTION AND STUDY FORMS

This section describes the study data collection and data management procedures and should include copies of all forms.

2.o.1 Source Documentation

Patient medical data are collected on source documents, such as lab reports, ECG tracings, medical records, study-specific source documents supplied by the Coordinating Center or sponsor, standardized test forms, and laboratory reports. Source documents are any documents on which study data are recorded for the first time.

To document study-specific data requirements, the source data are transcribed to a paper case report form (CRF) or entered into an electronic case report form (eCRF).

All study documents must be retained by the study investigator as described in Section 2.p.5. The following are considered participant file documents:

- case report forms
- data correction forms
- workbooks
- source documents (e.g., lab reports, ECG tracings, x-rays, radiology reports, etc.)
- signed participant consent forms
- questionnaires completed by the participant

This section describes how the source documentation should be maintained for the study.

2.o.2 Study Forms

This section details how study forms, also called case report forms (CRFs), are to be administered on a visit and question-by-question basis. Each of the study forms is included in this section with explanatory comments.

The section also identifies the person responsible for producing and distributing forms, how the forms are packaged or placed in a binder for each participant, how they are to be maintained, and who should be contacted in the event that additional forms are needed. In addition, a list of all study forms and the collection schedule are included.

2.o.3 Data Flow

It is the site's responsibility to ensure that all forms are complete. This section identifies the disposition of study forms. For example, in studies with Coordinating Centers, the forms are transmitted to the Coordinating Center on a schedule. This section should discuss the disposition of forms, as relevant, the schedule, and which copies of forms are to be maintained at the site and which are to be submitted for data entry. In addition, the section describes the data flow, data entry, and data correction procedures.

2.o.4 Retention of Study Documentation

The length of time all study files are to be maintained is specified in this section. NIH policy requires that studies conducted under a grant retain participant forms for three years, while studies conducted under contract must retain participant forms for seven years. Researchers should pay special attention to studies involving children, as study documentation retention procedures are often longer in duration and more comprehensive. The FDA individual IRBs, institutions, sponsors, countries, and states may have differing requirements for record retention; investigators should adhere to whichever requirements are most rigorous.

Investigators should retain forms and all other study documents for the longest applicable period. This period should be stated in the MOP.

2.o.5 Administrative Forms

The MOP should contain a complete set of administrative forms. Administrative forms assist study documentation and may include the following, as relevant:

Facsimile Transmittal Sheet serves as a cover page for all faxes, as required by a study.

Telephone Contact Log serves as a record of all conversations regarding the study and study participants.

Screening Log is a record of all individuals who are screened for participation in the study. It should be arranged chronologically and be kept up to date as discussed above in Section 2.d.1.

Record of Request for Exemption to Entry Criteria is used to document a participant's exemption to an entry criterion.

Participant Identification List records each participant's name, medical record number, study identification number and/or randomization number, and study entry and exit dates. The information is confidential and should be maintained in a secure location apart from forms and data files at the study site. The information contained in the list must be maintained by the site for a period stipulated by the governing body.

Study Drug Accountability Record is maintained in the Pharmacy by the research pharmacist and must not be shared with other members of the study team.

Record of Destruction of Clinical Product is a log used to document destruction of any unused study drug. The date, time and number of vials incinerated are recorded in the log. The log should be attached to the Study Drug Accountability Record.

CRF Transmittal Sheet serves as a cover page for each packet of CRFs submitted for data entry. It provides an inventory of the forms that are included in each mailing for mailed forms.

Signature Log contains the signature of all members of the site study team. It is the responsibility of the Principal Investigator and/or Clinical Research Coordinator to:

- designate individuals approved to make form entries and changes
- note the date when any study team member is removed from the team for any reason

Site Visit Log records individuals visiting the site. The most common reasons for visits are: site initiation, monitoring, training, and close-out.

Some of these forms may have been superceded by automated logs.
The message is that *study procedures must be documented.* In multisite studies, the more clearly that procedures are defined, the greater the likelihood that study documentation and data collection will be uniform across sites.

2.o.6 HIPAA Procedures

The Health Insurance Portability & Accountability Act (HIPAA) has guidelines for investigators pertaining to protection of participant confidentiality. Investigators should review information provided in Impact of the HIPAA Privacy Rule on NIH Processes Involving the Review, Funding, and Progress Monitoring of Grants, Cooperative Agreements, and Research Contracts (http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html) and contact their appropriate institutional officials to learn how the Privacy Rule applies to them, their organization, and their specific research project. Another helpful source is Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, NIH Publication 03-5388, which can be found at http://privacyruleandresearch.nih.gov. Written procedures to address issues pertaining to privacy and confidentiality of human participants in accordance to HIPAA regulations should be developed.

2.P DATA MANAGEMENT

This section describes the data management approach that will support the study and details how data are to be edited and corrected. For studies that involve a large number of sites and/or participants, the investigators may wish to consider a computerized approach.

Whether using a computerized approach or manual procedures, one should consider utilizing systems or procedures that encompass the following functions:

- ***Data Tracking*** - to provide the status of participant enrollment, number of forms completed at the sites, and number of forms transmitted to a Coordinating Center or lead site, as appropriate.
- ***Randomization*** - of participants to treatment arms.
- ***Data Entry*** - that is easy to use and minimizes errors, such as using screens that are facsimiles of the forms.
- ***Data Editing*** - that identifies out-of-range and missing entries, errors in dates (e.g., first treatment date precedes protocol start date), and logical inconsistencies (e.g., protocol specifies an examination before randomization, but there is no examination form).
- ***Updating module*** - to correct data and maintain an audit trail of all changes to the data
- ***Reporting*** - to describe and account for participants accrued, entered, completed, etc.
- ***Export module*** - to transmit data to statistical analysis packages (i.e., SAS).

Investigators should involve staff or colleagues with data management experience to assist with the determination of the data flow, transfer of data from sites in a multicenter study, handling of error identification and resolution, identification of useful reports, and deriving a frozen analytic database from edited or "clean" records. These areas should be discussed in this section.

As relevant, the MOP should include a description of the computer system used to support the study and a copy of the User's Guide.

Investigators should be aware that if they are conducting studies that will also be submitted to the FDA, the systems will need to be documented and validated. Guidance for electronic systems is found on the FDA Web site, *Title 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures* (http://www.fda.gov/ora/ compliance_ref/part11/Default.htm).

2.Q QUALITY CONTROL PROCEDURES

The integrity and credibility of the study depends on factors such as ensuring adherence to the protocol, obtaining complete follow-up information on all participants enrolled, and using quality control measures to establish and maintain high standards for data quality. The quality control (QC) plan should be developed before the study starts and should be implemented over the life of the study. It may include standard operating procedures (SOPs), data and forms checks, monitoring, routine reports, and correction procedures. This section should detail the various aspects of the plan and describe any training and certification procedures.

2.q.1 Standard Operating Procedures

One aspect of site quality control is standard operating procedures (SOPs). SOPs describe a site's generic procedures such as the maintenance of a screening log or quality control.

2.q.2 Data Form Checks

Data and forms checks depend upon data flow and computer procedures. However, data QC checks may specify the following types of checks:

- All data received from part centers
- No missing forms/data
- Unique identification (ID) number for each study participant that is consistent across all forms and visits
- Correct numbers in the site ID and participant's ID number
- Legible data
- Consistent and logical dates over time
- Data within acceptable ranges
- Data consistent across forms and visits
- All fields of a "completed form" actually completed or reason for no data noted
- All required forms completed or reason for no data noted.

2.q.3 Double Data Entry

In recent years, there have been several articles written on the value of double data entry. While conventional wisdom used to insist upon double data entry, it is recognized that it may not be necessary, especially if the data entry system provides edits as data are entered. Double data entry is still recommended for cases in which data entry staff enters data “heads down” or with no edits flagged as the data are entered.

2.q.4 Monitoring

Site monitoring typically takes place through periodic site visits conducted during the course of the study. The frequency of visits is dependent on the site's performance and the number of participants enrolled.

The purposes of monitoring visits are to:

- assure the rights and safety of participants
- confirm that study conduct follows the guidelines of Good Clinical Practice (GCP)
- assure maintenance of required documents
- verify adherence to the protocol
- monitor the quality of data collected
- assure accurate reporting and documentation of all AEs

During the monitoring visits, the data recorded on the study forms are reviewed and verified against source documents to assure:

- informed consent has been obtained and documented in accordance with NIH regulations
- the information recorded on the forms is complete and accurate
- there are no omissions in the reports of specific data elements
- missing examinations are indicated on the forms
- participant disposition at study exit is accurately recorded

The investigator must allow the clinical monitor access to all study documents, including informed consent forms, drug accountability records, and source documents, including pertinent hospital or medical records.

2.q.5 Reports

Once a study begins, routine reports prepared for the Principal Investigator or by the Coordinating Center or lead center in multi-site studies, are an important QC tool. Monthly reports may describe participants enrolled by site and in aggregate. Enrollment reports can describe participants screened, enrolled, refused participation, completed, discontinued treatment, and lost to follow-up. Monthly reports can also describe adverse events and serious adverse events. Administrative reports can enumerate the forms completed, entered, and missing and/or erroneous data and forms.

Reports are also provided to the DSMB. While DSMBs can specify the format and content of the reports they wish to receive, the reports are generally similar to the above.

2.R POLICIES

The MOP also contains the study's policies, such as confidentiality and publication policies.

2.r.1 Confidentiality Procedure

It is the responsibility of the study leadership to outline and enforce participant confidentiality and data security guidelines for the study. Study staff should be instructed in their responsibilities regarding data safeguards and cautioned against the release of data to any unauthorized individuals before they are allowed access to any study data.

The following is a list of study participant confidentiality safeguards:

- ***Data flow procedures*** - participant identifying information should not be transmitted from clinical site to the Coordinating Center.
- ***Electronic files*** - participant identifying information stored electronically should be maintained in an enciphered form or in a separate file.
- ***Forms*** - forms or pages containing personal identifying information should be separated from other pages of the data forms.

- ***Data listings*** - participant name, name code, hospital chart or record number, or other unique identifiers, such as Social Security number, should not be included in any published data listing.
- ***Data distribution*** - internally utilized data listings that contain participant name, name code, or other identifiers easily associated with a specific participant should not be distributed.
- ***Data disposal*** - computer listings that contain participant identifying information should be disposed of in an appropriate manner.
- ***Access*** - participant records stored in the data center should not be accessible to persons outside the center without the express written consent of the participant.
- ***Storage*** - study forms and related documents retained both during and after study completion should be stored in a secure, fireproof location.

If computers are used to store and/or analyze clinical data, sponsors should address the following elements of computer security to ensure that the data remain confidential:

- ***Passwords*** - Passwords provide limitations on general access to the systems and to the functions that individuals can use on the system. Passwords should be changed on a regular basis.
- ***User Training*** - Study staff with access to clinical computer systems should be trained in their use and in related security measures. Training should include explanations of how to access the system and a discussion of the need for, and importance of, system security.
- ***System Testing*** - Prior to the use of a new computer system, and if it is modified, the system should be tested to verify that it performs as expected. Testing should verify that the password approach to system access performs as intended.

- ***System Backups*** - Backup copies of electronic data should be made at specified intervals. Backups should be stored in file cabinets or secure areas with limited access. Storage areas should have controlled temperature and humidity so that the backup tapes are not damaged.

2.r.2 Publications

Investigators have a responsibility to the public to make study results available as soon as possible. The MOP should detail the publication policy so that data are not released inappropriately, authorship is predetermined, and manuscripts are subjected to rigorous review before they are submitted for publication.

2.S MOP MAINTENANCE

This section describes the procedures for updating and distributing updated MOP versions, as well as staff responsible for this activity. The MOP should be reproduced and distributed to appropriate staff in loose-leaf form. Each page of the MOP should be numbered and dated and should display a version number to facilitate any changes and/or additions. The MOP may serve as a history of the project, documenting the time and nature of any changes in procedures and policies.

The MOP should be continuously reviewed by study staff to ensure that the operating procedures described are accurate. If any procedures have been changed or modified, the MOP should be updated and the appropriately modified pages distributed, with instructions, for replacement in the MOP.

3.0 SUMMARY

The development of a study MOP is an important process that yields a product critical to assuring that a study will yield high quality results. Development of the MOP forces investigators to consider the details of a study and to develop procedures that are understood and can be followed uniformly by multiple clinical centers.

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RELEVANT WEB SITES

NINDS, NIH:

www.ninds.nih.gov/funding/clinical_trials/protocol.htm
(NINDS protocol template)
www.ninds.nih.gov/funding/clinical_trials/dsm_guidelines.htm
NINDS data and safety monitoring board guidelines
www.ninds.nih.gov/funding/clinical_trials/toolkit.htm
(NINDS' "tool kit" for investigators interested in performing NINDS-sponsored clinical research, including the above and links to other sites)

NIH:

http://ohrp.osophs.dhhs.gov/polasur.htm
(Office of Human Research Protections' Regulations on conducting research with human subjects)
http://www.nih.gov/sigs/bioethics/IRB.html
(Bioethics Resources on the Web)
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-040.html
(Guidance on financial conflicts of interest and research objectivity for IRBs and investigators)
http://www.ccc.nih.gov/ccc/protomechanics/index.html
(Guide to preparing a research protocol from the Warren G. Magnuson Clinical Center at NIH)
http://ohsr.od.nih.gov/info/finfo_6.php3
(Guidance for writing informed consent documents from the NIH Office of Human Subjects Research, which supports NIH intramural studies)

DHHS Office for Civil Rights - HIPAA Information:

http://www.hhs.gov/ocr/
http://privacyruleandresearch.nih.gov
(*Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule)*

Food and Drug Administration (FDA):

http://www.fda.gov/oc/gcp/regulations.html
(FDA Good Clinical Practice regulations)
http://www.fda.gov/cder/
(FDA Center for Drug Evaluation and Research)
http://www.fda.gov/cber/guidelines.htm
(FDA Center for Biologicals Evaluation and Research)
http://www.fda.gov/ora/compliance_ref/part11/Default.htm
(FDA regulations on electronic records and electronic signatures)
http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr312_00.html
(FDA application for an Investigational New Drug)
http://www.fda.gov/oc/ohrt/irbs/default.htm
(FDA Guidelines for protection of human subjects)

The following notices are guidance provided periodically to investigators by NIH on specific topics:

Gene Therapy, Stem Cells and Fetal Tissue:
http://grants.nih.gov/grants/policy/gene_therapy_20000307.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-050.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-026.html

Information Required in NIH Grant Applications:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html
http://grants.nih.gov/grants/guide/notice-files/not98-024.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html

NIH Policies for Monitoring Clinical Research:
http://grants.nih.gov/grants/guide/notice-files/not99-044.html
http://grants.nih.gov/grants/guide/notice-files/not98-084.html.
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html.
http://grants.nih.gov/grants/guide/notice-files/not99-107.html.
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html